

Study adds to understanding of respiratory syncytial virus disease

By Eddy Ball

A new study, funded in part by NIEHS, offers insight into the network of mechanisms involved in triggering a life-threatening respiratory disease in infants, respiratory syncytial virus (RSV) bronchiolitis, which is an important public health issue worldwide.

The result is what researchers describe as a plausible definition of the mechanisms involved in the interaction of environmental, genetic, epidemiological, and immune factors in the development of the disease in infants. The study takes into account the broad range of environmental factors, which include the effects of viral load, compounding bacterial and irritant exposures, and socioeconomic status on host susceptibility.

The pan-American team of 43 scientists also presents new evidence related to the hygiene hypothesis, which suggests that over-sanitizing the environment doesn't necessarily lead to better outcomes in every aspect of an infant's health. Avoiding some level of exposure may, in fact, interfere with conditioning of the immune response to infection and worsen disease.

For one group of middle class children with variations in the gene encoding toll-like receptor 4 (TLR4), cleaner living seemed to have little impact on the disturbing rates of their hospitalization, which approached those of extremely premature babies.

International team science at work

Co-led by NIEHS lead researcher [Steven Kleeberger, Ph.D.](#), and his long-time colleague [Fernando Polack, M.D.](#)

(<http://vucenter.org/member/fernandopolack>)

, an infectious disease specialist with appointments at Vanderbilt University and the Infant Foundation in Argentina, the [paper](#)

(<http://www.ncbi.nlm.nih.gov/pubmed/25555213>)

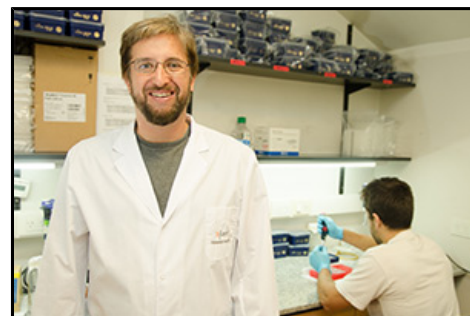
appeared in the February issue of the Journal of Clinical Investigation.

"We looked at hundreds of infants from different environments, performed a battery of tests on a wide range of molecules, and confirmed our findings in a mouse model of RSV disease," Kleeberger said. "While controversies remain about RSV, we've helped to answer a number of important questions and identified a novel group at high risk for developing a severe form of the disease."

Through a careful process of elimination, the team narrowed down the influences of a number of inflammatory proteins to identify the specific cytokines involved. The researchers also examined candidate variables that might affect the severity of RSV bronchiolitis, including levels of the virus in respiratory secretions, which did not show a significant association.



Kleeberger took advantage of collaborations with Polack and his large cohort of children in Argentina to add considerable power to work on infant respiratory diseases. (Photo courtesy of Steve McCaw)



Polack, shown in his lab in Buenos Aires, led access to patients at four hospitals in different regions the city, two of them separated by more than 40 miles. (Photo courtesy of Fundacion INFANT)

not show a significant association.

Pioneering tie-in of environment and RSV

According to the researchers, this is the first study of its size and kind to explore the role of environmental factors in RSV pathogenesis. The findings point to involvement of environmental endotoxin, Tlr4 genotype, and cell polarization of T helper type 2 (Th2) as influencing disease severity. They also gained insight into the immune mechanism regulating differential susceptibility to RSV disease severity.

Their findings, the team concluded, point to the importance of exploring modulation of these target molecules. They also speculated that additional research with Tlr4 genotype infants could lead to preventive interventions aimed at virus neutralization and novel anti-Th2 approaches to help protect children at highest risk of severe disease.

Along with NIEHS funding, which included the Director's Challenge Award Kleeberger and Polack received in 2006 (see [story](#)), the study was supported by the National Institute of Allergy and Infectious Diseases and the Bill and Melinda Gates Foundation.

The team included scientists affiliated with 17 different groups in the U.S. and Argentina, and a hospital in Brazil. Two additional NIEHS scientists, biologist [Jacqui Marzec](#) and biostatistician [Min Shi, M.D., Ph.D.](#), were also part of the team.

Citation: Caballero MT, Serra ME, Acosta PL, Marzec J, Gibbons L, Salim M, Rodriguez A, Reynaldi A, Garcia A, Bado D, Buchholz UJ, Hijano DR, Coviello S, Newcomb D, Bellabarba M, Ferolla FM, Libster R, Berenstein A, Siniawski S, Blumetti V, Echavarria M, Pinto L, (http://www.ncbi.nlm.nih.gov/pubmed/25555213)
2015. TLR4 genotype and environmental LPS mediate RSV bronchiolitis through Th2 polarization. J Clin Invest 125(2):571-582.



Marzec is a member of Kleeberger's Environmental Genetics Group at NIEHS. (Photo courtesy of Steve McCaw)



Shi is a member of the NIEHS Biostatistics and Computational Biology Branch, specializing in gene-environment, gene-gene interaction, and pathway-based analysis. (Photo courtesy of Steve McCaw)

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